

to lower efficacies and increased the proportion of subjects shedding resistant viruses. As an example, a 75-mg/day prophylaxis regimen initiated 2 days before inoculation and stopped 2 days after inoculation would decrease the efficacy to 18% and increase the proportion of subjects shedding resistant virus to 8%. Conclusions: Using a simulation model based on H1N1 infection data, we were able to reproduce drug-resistant emergence rates similar to those reported in the literature. Based on our simulation results, we recommend that current prophylaxis regimens should be avoided to limit resistance emergence. Initiation of treatment during the incubation period should be restricted to subjects prone to develop severe cases and should use high doses (at least 150 mg per intake) and frequent intakes (bid or tid) for a longer period (10-15 days) in order to decrease the risk of resistant virus emergence and to preserve high efficacies.

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Susceptibility of influenza B viruses to neuraminidase inhibitors: findings from the first 4 years (2008–2012) of the global Influenza Resistance Information Study (IRIS)

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Background: Type B influenza virus infections continue to account for a substantial proportion of clinical illness. Little is known about comparative disease profiles by virus lineage. A global observational trial (the Influenza Resistance Information Study or IRIS; NCT00884117) was initiated to study neuraminidase inhibitor (NAI) susceptibility and the clinical and virological course of influenza in treated and untreated patients. **Materials and Methods:** Patients in the northern and southern hemispheres (USA, France, Germany, Poland, Norway, Hong Kong, Australia) with influenza-like illness and/or a positive rapid influenza test result were enrolled. Throat/nasal swabs were performed on Days 1, 3 (self-swab), 6 and 10 and tested for influenza A and B viruses by RT-PCR. Influenza-positive samples collected on Days 1, 6 or 10 were cultured and subsequently sequenced (HA and NA) and phenotypically tested for NAI susceptibility. The lineage of B viruses was determined from sequencing. Clinical information, including the scoring of seven influenza symptoms (scale: 0 [absent], 1 [mild], 2 [moderate], 3 [severe]), was recorded on diary cards by the patient or the patient's legal guardian (Days 1–12). Symptoms were also assessed by the investigator at each visit. The decision to prescribe an NAI was left to the physician's discretion. **Results:** In the first 4 years of IRIS (December 2008 to March 2012), 2262 influenza-positive (RT-PCR) patients were enrolled, of whom 697 presented with a type B influenza virus infection (564 Victoria, 98 Yamagata, 35 undetermined lineage). Most type B patients (402; 58%) were children aged < 13 years. A total of 330 (47%) type B patients were treated with oseltamivir (as monotherapy) within 2 days of symptom onset; a further 26 started oseltamivir 2 days after symptom onset. Eleven patients received zanamivir, one received amantadine and another received rimantidine. A total of 328 (47%) did not receive any influenza antiviral. Symptoms were mild to moderate on Day 1 (mean total score: 12.8, treated; 12.9, untreated), and the mean temperature on Day 1 was 38.2°C. All viruses obtained at baseline or post-baseline were susceptible to NAIs: mean (SD) IC₅₀ values for oseltamivir were 4.8 nM (2.5 nM) and 5.5 nM (2.3 nM) for the Victoria and Yamagata viruses, respectively; the corresponding values for zanamivir were 2.0 nM (1.4 nM) and 2.9 nM (1.6 nM), respectively. No known NAI resistance mutations were detected by NA or HA population sequencing. The proportion of RT-PCR-positive patients on Day 6 was 130/309 (42.1%) for patients treated with oseltamivir and 152/312 (48.7%) for untreated patients. In Kaplan–Meier analyses, no significant differences in median time to influenza RNA clearance were found between oseltamivir-treated and -untreated patients, either in adults or children. The time to symptom resolution (all symptom scores ≤ 1) was 5 days (95% CI, 4–5 days) in oseltamivir-treated children and 6 days (95% CI, 5–6 days) in untreated children (*P* = .026), but no significant difference in symptom resolution time was found in adults (Kaplan–Meier analysis). **Conclusions:** Analysis of type B influenza viruses obtained globally between 2008 and 2012 showed that all pre-treatment B/Victoria and B/Yamagata viruses were susceptible to oseltamivir and zanamivir. Moreover, no resistant viruses were detected during treatment. Given the non-randomised

design of this study, no definitive conclusions can be drawn with regard to the clinical benefit of oseltamivir in patients infected with type B influenza viruses.

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Persistence of influenza A(H3N2) viruses following oseltamivir therapy in nursing homes in the Netherlands

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Background: Influenza viral load dynamics and emergence of antiviral resistance during oseltamivir therapy and prophylaxis have mainly been studied in previously healthy adults and children and immunocompromised individuals with influenza. This information is sparse on one of the main target populations for antiviral use if influenza prevention by vaccination fails: frail elderly residing in nursing homes. Therefore, we analysed specimens from nursing home residents in the Netherlands collected during oseltamivir therapy and prophylaxis. In addition, we aimed to assess transmission of (antiviral resistant) viruses by virus sequence analysis. **Materials and Methods:** The study was performed during the 2011/2012 and 2012/2013 winter seasons. Oseltamivir therapy was offered to residents with influenza-like illness (ILI) with or without laboratory diagnostic results. Oseltamivir prophylaxis was offered to residents without respiratory symptoms as soon as influenza virus infection in another resident was confirmed by laboratory testing. From residents on therapeutic use, specimens (combined nose and throat swabs) were requested at the start and end of therapy (day 5). From residents on prophylaxis, end-of-prophylaxis specimens were requested (day 10). RT-PCR-positive specimens were further characterised by virus isolation and phenotypic antiviral susceptibility assay; sequencing of the haemagglutinin (HA), neuraminidase (NA) and matrix protein genes directly from the clinical specimen; and single nucleotide polymorphism (SNP) real-time RT-PCR for detection of mutations resulting in oseltamivir reduced susceptibility-associated amino acid substitutions E119V and R292K in the NA of A(H3N2) viruses. **Results:** Of 49 residents with ILI, start-of-therapy specimens were obtained, 33 of which were positive for A(H3N2) influenza virus. An end-of-therapy specimen was obtained from 37 residents, 10 of which were positive for A(H3N2) influenza virus. Paired specimens were available for 28 residents, of whom 19 were confirmed to be infected with A(H3N2) influenza at the start of therapy. One of these 28 residents had an A(H3N2)-positive specimen only at the end of therapy. Twelve of nineteen residents (63%) had cleared the infection upon resampling, whereas 7 of 19 residents (37%) had A(H3N2)-positive specimen at both the start and end of therapy. In five of these cases, the viral load decreased (mean Ct increase of 6.9; range 4.1-9.8), whereas in two cases the viral load increased (Ct decreases of 2.1 and 4.3). By the end of therapy, one resident with a decreasing viral load was shedding a virus containing the R292K amino acid substitution, whereas the start-of-therapy specimen contained 292R. NA sequence analysis, SNP detection and phenotypic analysis did not show emergence of viruses with a resistance marker or reduced inhibition by oseltamivir for the other six residents with positive end-of-therapy specimens. Of 32 residents who received oseltamivir prophylaxis, 1 was found positive for A(H3N2) influenza virus at day 5 following development of ILI and 2 were found positive for influenza virus type B lineage B/Yamagata/16/88 at day 10 (end of prophylaxis). Sequence analysis of the M protein of 17/43 detected A(H3N2) viruses showed a subset of viruses with the S31N and V27I amino acid substitution M2-blocker resistance markers, which is a unique combination. Uniqueness was confirmed by mutations in the NA and HA genes of these viruses compared with those of other sequenced A(H3N2) viruses. These unique viruses originated from two locations of one nursing home about 5 km apart. **Conclusions:** The high proportion of A(H3N2)-positive end-of-therapy specimens (37%) suggests that a 5-day course of oseltamivir therapy for nursing home residents may not be adequate to clear the influenza virus completely. Nevertheless, the R292K substitution in the NA of the influenza virus was found for only one resident receiving oseltamivir therapy, suggesting a relatively high barrier for the A(H3N2) virus to attain this or other substitutions associated with reduced